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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/513,997	02/26/2000	John J. Harrington	5817-7Q	9509

959 7590 10/05/2004

LAHIVE & COCKFIELD, LLP.
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BOSTON, MA 02109

EXAMINER	
SHUKLA, RAM R	
ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 10/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/513,997	HARRINGTON ET AL.	
	Examiner	Art Unit	
	Ram R. Shukla	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 July 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *108-118* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *108-118* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicants' response filed 7/16/04 has been received and entered.

2. Claim 119 has been cancelled.

3. Claims 108-118 are pending in the instant application.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 108-119 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for reasons of record set forth in the previous office action of 1/16/04.

Response to Arguments

Applicant's arguments filed 7/16/04 have been fully considered but they are not persuasive.

Applicants argue:

> overexpresses the protein". Applicants submit that specific guidance was not necessary as will be discussed in this Response.

However, these arguments are not persuasive because to an artisan to practice a claimed invention, specific guidance has to be present in the specification.

Court states, "It is true, as Genentech argues, that a specification need not disclose what is well known in the art. See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc. , 802

F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement." (See Brenner v. Manson, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966))

In the instant case, claimed invention broadly encompasses an in vivo method of over expressing a desired protein encoded by a desired endogenous gene or a portion thereof into a an animal by introducing a non-homologously recombinant cell in which a vector comprising a transcriptional regulatory sequence is integrated such that the transcriptional regulatory sequence of the vector is operably linked to the desired endogenous gene. As has been discussed in the previous office action, the specification does not provide any specific guidance for practicing the claimed method. It is noted that applicants ignored the discussion in the previous office action (pages 3-4 of the office action of 1/16/04) lack of teachings in the instant specification. As was discussed in the previous office action, based on the teachings of the specification, an artisan could not know what was contemplated by the applicants. Applicants list 15 references (listed in table on page 7 of the response) and argue that they contemplated everything taught in the these references and rest of what was available in the art, however, there is no evidence of record that applicants contemplated any of these methods (discussed in the references). Applicants argue:

References Reporting Recombinant Protein Expression *In Vivo* Demonstrate That RAGE* Cells Would Also Have Been Useful to Express Protein *In Vivo*

The arguments are misplaced and irrelevant because utility is not the issue here, rather enablement is the issue. Applicants perhaps ignore the fact that the

rejection of 2/14/01 is not the pending rejection, rather rejection of 1/16/04 is the current pending rejection.

On pages 7, applicants list cells, gene product, host, mode of administration in different references and argue that examiner did not discuss all the references Applicants also argue:

> Nine of these references report using *exogenous* coding sequences. The Examiner only discusses Chen and Garver. Both Chen and Garver introduced exogenous coding sequences.

Again applicants ignore what was discussed in the office action. The examiner collectively addressed all the references on page 7 last paragraph continued on page 8 and therefore, discussion of each reference individually was not necessary. The discussion is reiterated below:

> Second, introduction of cells into an animal for any non-therapeutic use, for example, producing antibody was not enabled because the specification as filed does not provide any specific guidance for practicing any non-therapeutic method and the methods taught in the art were different from the method claimed in the instant and the general teachings of the art could not be applied. For example, the arts by Brodeur, Kints, Stewart, Shaw, Chen, Garver, Bronson, McNiece, Treco, Ishihara et al could not provide enabling support for the instantly claimed method because these articles describe use of specific cells and the method steps used in these articles could not be compared to the method claimed. For example, Chen and Garver articles are examples of ex vivo therapy and as discussed above the art of ex vivo therapy was unpredictable. It is emphasized that the method of Chen and Garver teach injection of cells transfected with a retroviral vector that expresses an exogenous gene, which is not the same as a cell in which the expression of an endogenous gene has been activated by introducing an exogenous promoter. Therefore, the expression pattern of a retroviral gene cannot be compared to the expression of an endogenous under the control of an exogenous promoter. It is noted that Anderson et al discussed the unpredictability of gene expression from retrovirally transduced cells.

. Next, under the subheadings "further issue, effective expression in vivo-non-human animals, introducing cells, cell maintenance in vivo ", Applicants argue

that Kay or Anderson or other references cited by the examiner do not support Examiner's position. Again, applicants discuss the deficiency of Anderson, but choose to ignore the real issue that the art of expressing a gene in vivo by providing recombinant cells to an animal was unpredictable at the time of the invention and that the specification of the instant application lacks any specific guidance for practicing the instantly claimed invention. Next, applicants discuss US 5,994,127 and 6,054,288 and that these references show survival of fibroblast engineered to express EP or hGH in vivo. However, these arts fail to establish that the method of expressing a gene in vivo by providing recombinant cells to an animal a routine method, in view of the unpredictability of the state of the art as discussed by the references cited in the previous office action of 1/16/04. As discussed in the previous office action (pages 7-8 of the previous office action) and reiterated below:

"It is reiterated that the specification except for single sentences regarding in vivo method does not provide how would an artisan of skill have practiced the claimed method. It is noted that since the cells used in the claimed invention are not related or similar to any other cells that are taught in the cited arts, the method used in these other unrelated art cannot be used to support the enablement or other readily apparent utilities. The specification has failed to provide any evidence where in the specification how to make and use the claimed methods have been described. Pages 7-9, 13, 16, 17, 29 and 35 of the 08/941223 provide cursory statements, such as "Alternatively the cells can be allowed to express the desired gene product *in vivo*" (page 7, lines 8-9); "The cells can be used to provide desired amounts of a gene product in vitro or in vivo, The gene product can then be isolated and purified if desired. It can be purified by cell lysis or from growth medium (as when the vector sequence contains a secretion signal sequence)" (page 8, lines 14-17). Applicants are arguing that such statements provide enabling disclosure for the claimed methods, however, it is not clear how an artisan of skill would have been able to practice the claimed method by following these cursory general statements.

In conclusion, it is emphasized that the specification does not teach any specific teaching for carrying out any in vivo method and since the introduction of recombinant cells into an animal for over expressing a protein was not routine in the art except for specific cells, an artisan of skill would have required undue experimentation to practice the claimed method."

the Examiner has established that the state of the art of a method of expressing a gene in vivo by providing recombinant cells to an animal was not routine

and was unpredictable and specific guidance was required to practice the method and such specific guidance was lacking in the specification of the instant application. In conclusion, applicants' arguments have failed to provide any substantive evidence to address the unpredictability of the state of the art of a method of expressing a gene in vivo by providing recombinant cells to an animal and that the specification provided specific teachings for practicing the claimed invention and therefore, the enablement rejection is maintained for reasons of record set forth in the previous office action of 1/16/04.

6. No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

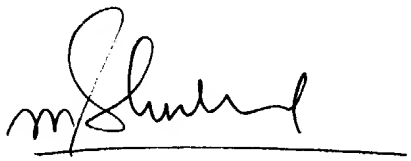
A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ram R. Shukla whose telephone number is (571) 272-0735 . The examiner can normally be reached on Monday through Friday

from 7:30 am to 4:00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached at (571) 272-0804. The fax phone number for TC 1600 is (703) 872-9306. Any inquiry of a general nature, formal matters or relating to the status of this application or proceeding should be directed to the Dianiece Jacobs whose telephone number is (571) 272-0532.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Ram R. Shukla, Ph.D.
Primary Examiner
Art Unit 1632



RAM R. SHUKLA, PH.D.
PRIMARY EXAMINER